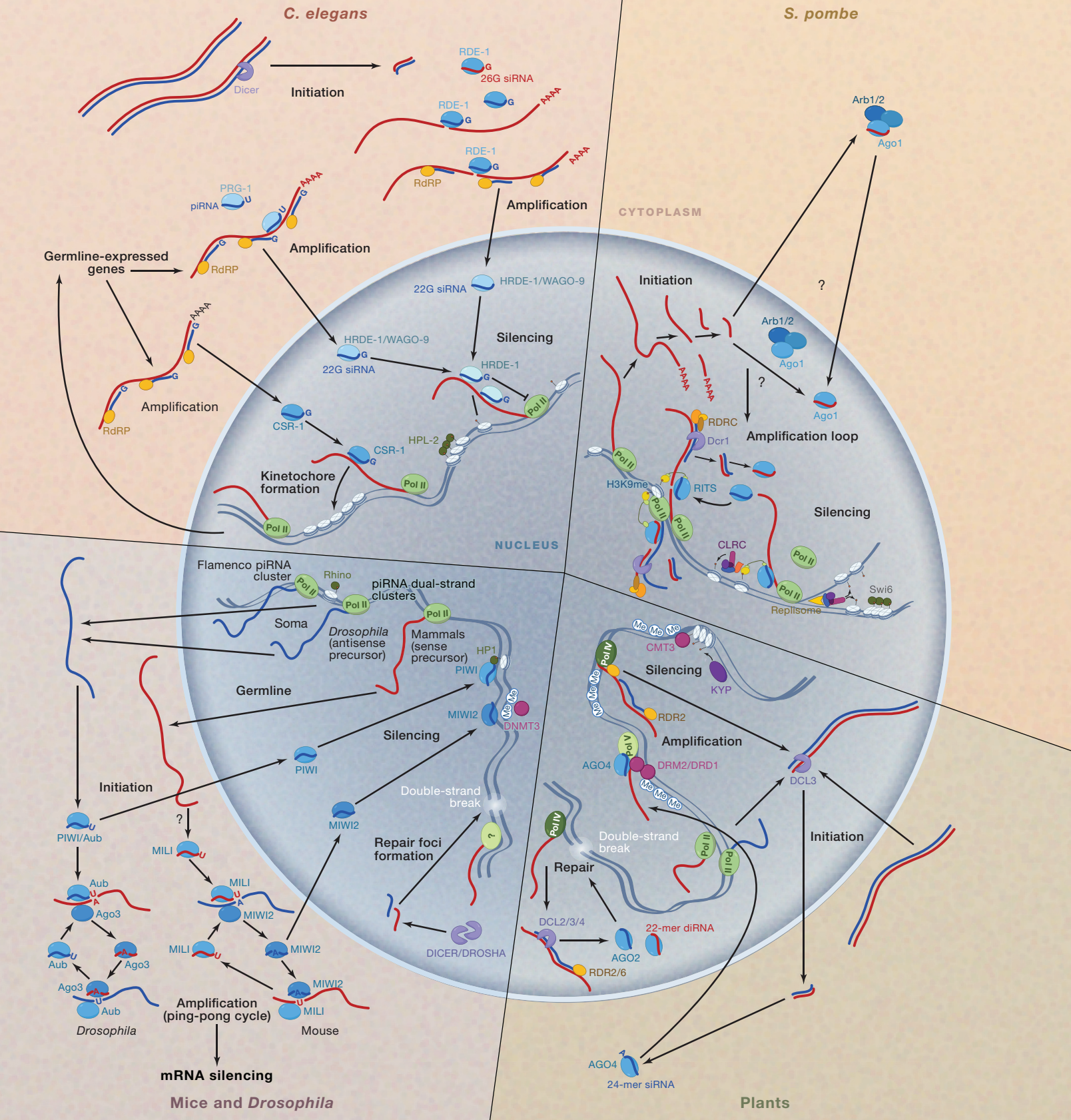
SnapShot: Small RNA-Mediated Epigenetic Modifications

Cell

Mikel Zaratiegui[1] and Robert A. Martienssen[2]
[1]Department of Molecular Biology and Biochemistry, Rutgers University, Piscataway, NJ 08854, USA
[2]Howard Hughes Medical Institute-Gordon and Betty Moore Foundation, Watson School of Biological Sciences, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA



 DOI http://dx.doi.org/10.1016/j.cell.2012.10.001 See online version for legend and references.

SnapShot: Small RNA-Mediated Epigenetic Modifications

Cell

Mikel Zaratiegui[1] and Robert A. Martienssen[2]
[1]Department of Molecular Biology and Biochemistry, Rutgers University, Piscataway, NJ 08854, USA
[2]Howard Hughes Medical Institute-Gordon and Betty Moore Foundation, Watson School of Biological Sciences, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA

The function of chromatin in transcriptional control and chromosomal architecture is regulated by a diverse set of RNA components in all eukaryotes. Chief among them is the participation of small RNA (sRNA) generated by the RNA interference (RNAi) machineries. The mechanisms that guide sRNA generation are diverse in different organisms, but they can be roughly divided in three steps. First, an initiation step generates an initial pool of primary sRNA from a double-stranded RNA (dsRNA) precursor processed by Dicer enzymes (in plants and *Caenorhabditis elegans*); degradation products of primary transcripts synthesized by RNA Pol II (in *Schizosaccharomyces pombe*); or processing of single-stranded precursors by unknown nucleases, resulting in PIWI-interacting sRNA (piRNA; in insects, mammals and *C. elegans*). The sRNA can also be inherited from a previous generation or received from other cells (in plants). These primary sRNAs bind to Argonaute proteins, which find their cognate targets by sequence complementarity. This recognition can lead to cleavage of the target by the slicer capable Argonautes and guides the second step that results in an amplification of the signal with accumulation of secondary sRNA. Amplification can involve the generation of dsRNA by RNA-dependent RNA polymerase (RdRP) activities on the Argonaute-targeted RNA, followed by Dicer processing (in plants and *S. pombe*), by direct generation of secondary sRNA by RdRP (22G siRNA in *C. elegans*), or by a series of cleavages in single-stranded RNA precursors, carried out in alternating order by PIWI clade Argonautes and other unknown nucleases (the ping-pong cycle, in insects and mammals). In the final step, Argonaute and PIWI-bound secondary sRNA can relocate to the homologous loci in the DNA by base pairing with nascent transcripts as they are synthesized by RNA Pol II (in *S. pombe* and *C. elegans*) and specialized RNA polymerases (RNA Pol IV and V in plants) and mediate recruitment of chromatin remodeling activities that can result in heterochromatin formation (methylation of histone 3 lysine 9 and binding of heterochromatin protein 1 [HP1] homologs), DNA methylation (in plants and mammals), and establishment of other types of chromatin domains like centromeric chromatin (in *C. elegans*). The RNAi machinery also directly protects genome integrity by facilitating DNA replication, by the re-establishment of heterochromatin in the wake of the replication fork, and by Dicer processing of transcription products that arise in the vicinity of double-strand breaks in the DNA that have a role in repair of the lesion (in plants and mammals). A similar phenomenon has been observed in the fungus *Neurospora*.

Conventions

RNA strand is represented in two different colors: red for sense and blue for antisense (or forward and reverse, respectively, in the case of noncoding RNAs). DNA is in light blue double strand, and cytosine methylations are represented by "Me." DNA-dependent RNA polymerases are green ovals and are identified where possible. Argonaute-type proteins are in shades of blue; RdRP proteins or complexes are in orange, and Dicer proteins are in magenta. Histone and DNA modification factors are in purple. When a particular residue in the sRNA is typical of a species (as in the 22/26-G RNAs in *C. elegans* and the 5′U and paired A signature of ping-pong-amplified piRNA); it is represented as a letter in the sRNA.

Abbreviations and Definitions

S. pombe: Ago1, Argonaute; Dcr1, Dicer; RDRC, RNA-dependent RNA polymerase complex; RITS, RNA-induced initiation of transcriptional silencing complex; CLRC, Clr4 methyltransferase complex; Swi6, HP1 homolog.
C. elegans: RDE-1, AGO clade Argonaute; RdRP, RNA-dependent RNA polymerase(s); PRG-1 and CSR-1, PIWI-clade Argonautes; HRDE-1/WAGO9, heritable RNAi defective/worm-specific Argonaute; HPL-1, HP1 homolog.
Insects: PIWI, Aub/Aubergine, Ago3, PIWI clade Argonautes; Rhino, HP1 homolog, needed for dual-strand piRNA cluster expression.
Mice: MILI/MIWI2, PIWI clade Argonautes; DNMT3, DNA methyltransferase.
Plants: DCL2/3/4, Dicer-like homologs; AGO2/AGO4, Ago-clade Argonautes; RDR2/6, RNA-dependent RNA polymerases; DRM2,CMT3, DNA methyltransferases; DRD1, SNF2 chromatin remodeler; KYP, Kryptonite H3K9 methyltransferase.

Acknowledgments

We would like to acknowledge Sam Guoping Gu for critical comments. R.A.M. was supported by NIH and NIGMS grant R01GM076396-05.

REFERENCES

Ashe, A., Sapetschnig, A., Weick, E.-M., Mitchell, J., Bagijn, M.P., Cording, A.C., Doebley, A.-L., Goldstein, L.D., Lehrbach, N.J., Le Pen, J., et al. (2012). piRNAs can trigger a multigenerational epigenetic memory in the germline of C. elegans. Cell *150*, 88–99.

Buckley, B.A., Burkhart, K.B., Gu, S.G., Spracklin, G., Kershner, A., Fritz, H., Kimble, J., Fire, A., and Kennedy, S. (2012). A nuclear Argonaute promotes multigenerational epigenetic inheritance and germline immortality. Nature *489*, 447–451.

Claycomb, J.M., Batista, P.J., Pang, K.M., Gu, W., Vasale, J.J., van Wolfswinkel, J.C., Chaves, D.A., Shirayama, M., Mitani, S., Ketting, R.F., et al. (2009). The Argonaute CSR-1 and its 22G-RNA cofactors are required for holocentric chromosome segregation. Cell *139*, 123–134.

Francia, S., Michelini, F., Saxena, A., Tang, D., de Hoon, M., Anelli, V., Mione, M., Carninci, P., and d'Adda di Fagagna, F. (2012). Site-specific DICER and DROSHA RNA products control the DNA-damage response. Nature *488*, 231–235.

Gu, S.G., Pak, J., Guang, S., Maniar, J.M., Kennedy, S., and Fire, A. (2012). Amplification of siRNA in Caenorhabditis elegans generates a transgenerational sequence-targeted histone H3 lysine 9 methylation footprint. Nat. Genet. *44*, 157–164.

Kim, V.N., Han, J., and Siomi, M.C. (2009). Biogenesis of small RNAs in animals. Nat. Rev. Mol. Cell Biol. *10*, 126–139.

Wei, W., Ba, Z., Gao, M., Wu, Y., Ma, Y., Amiard, S., White, C.I., Rendtlew Danielsen, J.M., Yang, Y.-G., and Qi, Y. (2012). A role for small RNAs in DNA double-strand break repair. Cell *149*, 101–112.

Matzke, M., Kanno, T., Daxinger, L., Huettel, B., and Matzke, A.J.M. (2009). RNA-mediated chromatin-based silencing in plants. Curr. Opin. Cell Biol. *21*, 367–376.

Shirayama, M., Seth, M., Lee, H.-C., Gu, W., Ishidate, T., Conte, D., Jr., and Mello, C.C. (2012). piRNAs initiate an epigenetic memory of nonself RNA in the C. elegans germline. Cell *150*, 65–77.

Zaratiegui, M., Castel, S.E., Irvine, D.V., Kloc, A., Ren, J., Li, F., de Castro, E., Marín, L., Chang, A.-Y., Goto, D., et al. (2011). RNAi promotes heterochromatic silencing through replication-coupled release of RNA Pol II. Nature *479*, 135–138.

  DOI http://dx.doi.org/10.1016/j.cell.2012.10.001